REMARKS

Claims 1 to 4 and 6 to 20 are in the application. Claim 5 has been cancelled. Claims 1, 3, 4, 6, 7, 8, and 11 have been amended. Claims 14 to 20 have been added. Support for the newly added claims and the amendments to the claims lie in the claims as originally filed, or in the specification on page 9, lines 20 to 32; pages 10, 11, and 12, lines 1 to 30. No new matter is believed added.

Rejection under 35 USC § 102

Claims 1 to 4 are rejected under 35 USC § 102(b) as being unpatentable over Zirkle et al., J. Med. Chem. (1962), Vol. 5, pg 341-56 (hereinafter "Zirkle I").

Claims 1 to 4 are also rejected under 35 USC § 102(b) as being unpatentable over Zirkle et al., US 2,800,478 (hereinafter "Zirkle II"). Applicant respectfully traverses these rejections.

Claim 1 has been amended to recite a composition of a compound of Formula (I) which is suitable for use in the respiratory tract of a human as a dry powder inhaled formulation.

The Zirkle et al. article and the Zirkle et al. patent do not describe pharmaceutical formulations, or pharmaceutical formulations suitable for inhaled use.

Therefore, in view of these remarks and amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC §102 over Zirkle I and Zirkle II is respectfully requested.

Rejection under 35 USC § 103

Claims 1 to 4 are rejected to under 35 USC § 103(a) as being unpatentable over Yu et al., Yaoxue Xuebao (1983), 18(10), pg 766-74.

Claims 1 to 4 are rejected to under 35 USC § 103(a) as being unpatentable over Ran et al., Yaoxue Xuebao (1984), 19(5), pg 361-6.

Claims 1 to 4 are rejected to under 35 USC § 103(a) as being unpatentable over Zhang et al., Yaoxue Xuebao (1985), 20(10), pg 752-8.

Claims 1 to 4 are rejected to under 35 USC § 103(a) as being unpatentable over Wu et al., Yaoxue Xuebao (1993), 3(1), pg 23-6.

Claims 1 to 4 are rejected to under 35 USC § 103(a) as being unpatentable over Zirkle et al., J. Med. Chem. (1962), 5, p 341-56.

Applicant respectfully traverses all of these rejections.

The USPTO has failed to provide copies of the references cited in this rejection and those additionally on the PTO-892 form that pursuant to their own requirements as specified in the Manuel §707.05(a). However, in response to telephonic communication with the Examiner, Applicants gratefully acknowledge the faxing of the Yu et al. 1983 article, the Ran et al. (1984) article and the Wu et al. (1993) article(s) cited herein. Applicants have not received a copy of the Zhange et al. (1985) article. Upon review of the three articles received, it appears that both the Examiner's Office Action and the PTO-892 fail to indicate if it is the full journal article (each in Chinese), or the English Abstract of these article(s) which form the basis of each of the rejections herein.

The USPTO Manuel §706.02 (II) which states that the Examiner must indicate if it is the abstract of the full text which is the basis of the rejection, and if the document is in a language other than English (as it the case here) a translation must be obtained (see excerpt below). Consequently, Applicants request clarification of the record as to specifically where in each of the cited references the rejection lies, and with particularity where as to each compound cited, by the Examiner. Applicants also request a translation of the articles to be supplied by the USPTO so as to allow Applicants to fully determine any issues of patentability.

II. RELIANCE UPON ABSTRACTS AND FOREIGN LANGUAGE DOCUMENTS IN SUPPORT OF A REJECTION

Prior art uncovered in searching the claimed subject matter of a patent application often includes English language abstracts of underlying documents, such as technical literature or foreign patent documents which may not be in the English language. When an abstract is used to support a rejection, the evidence relied upon is the facts contained in the abstract, not additional facts that may be contained in the underlying full text document. Citation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document are prior art. See *Ex parte Jones*, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001) (unpublished).

To determine whether both the abstract and the underlying document are prior art, a copy of the underlying document must be obtained and analyzed. If the document is in a language other than English and the examiner seeks to rely on that document, a translation must be obtained so that the record is clear as to the precise facts the examiner is relying upon in support of the rejection. The record must also be clear as to whether the examiner is relying upon the abstract or the full text document to support a rejection. The rationale for this is several-fold. It is not uncommon for a full text document to reveal that the document fully anticipates an invention that the abstract renders obvious at best. The converse may also be true, that the full text document will include teachings away from the invention that will preclude an obviousness rejection under 35 U.S.C. 103, when the abstract alone appears to support the rejection. An abstract can have a different effective publication date than the full text document. Because all patentability determinations are fact dependent, obtaining and considering full text documents at the earliest practicable time in the examination process will yield the fullest available set of facts upon which to determine patentability, thereby improving quality and reducing pendency.

Consequently, the rejection is improper for failure of the USPTO to follow its own requirements.

Applicants respectfully request that the USPTO forward the necessary translations and provide Applicants with an additional 30 days to respond to the outstanding rejection in this application.

However, in an attempt to be responsive to the Examiner's rejections and using the accompanying 3 English abstracts it would appear that the basis of the obviousness argument(s) is that the compounds of Yu et al. (1983) are "analogous compounds"

which possess anticholinergic activity. The Ran et al. abstract discloses a similar statement, e.g. "Most of I showed anticholinergic activity in mice."

The Wu et al. article is also similar in that it states "The anticholinergic actions of all these compounds were tested preliminarily in mice and the compounds exhibited certain actions". Applicants can not determine with any clarity whether the compounds in any of these articles, are as stated by the Examiner, actually present and described therein without a translation. However, from a cursory review the compounds described in these references do not appear to be quaternary salt forms as required by Claim 1 herein.

This does not address that the claims, as amended, are directed to a particular form of a composition, e.g. a dry powder inhalation composition. This is in contrast to liquid inhaled composition such as a solution or suspension, for inhalation. The devices claimed in claims 9 and 10 and newly added claims 18 to 20 are specific to "powder" compositions for use therein.

The Zirkle et al. Med Chem. article additionally does not disclose, or discuss in any manner a combination of the compound(s) disclosed therein with a pharmaceutically acceptable carrier or excipient, e.g. as pharmaceutical composition. It does not teach how one would formulate the compounds for delivery to a human by any accepted route of administration, e.g. orally, topically, intravenously, intramuscularly or inhaled.

The Examiner has not provided any motivation to direct the skilled artisan to make a pharmaceutical formulation of the compounds of Yu, Ran, Wu or Zirkle as a dry powder inhalable formulation. Consequently, the Examiner and the USPTO have failed to make out a *prima facie* case of obvious.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC §103 over Zirkle et al. is respectfully requested.

Rejection under 35 USC § 112

Claims 5 to 13 are rejected under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to alter the gene expression and therefore to treat any and all known of unknown diseases. Applicants respectfully traverse this rejection.

It is unclear why it would be necessary for Applicants composition to " alter the gene expression and therefore to treat any and all known of unknown diseases". Applicant's compounds are antagonists of a receptor and act accordingly thereby. Clarification of this statement is respectfully requested.

The Examiner cites the various In re Wands factors and correctly comments upon the nature of Applicants invention on page 4, 1rst ¶ of the Office Action. What is unclear is the Examiners conclusion that "more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regard to therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject".

Muscarinic antagonists have been known for many decades. The very patent and publication of Zirkle et al. as cited by the Examiner readily demonstrate early use of this antagonism. There are large numbers of patents granted by the USPTO on muscarinic antagonists. There are oral compounds commercially available having anticholinergic activity, as well as inhaled compounds, depending upon which of the receptors that one wishes to antagonize. One of skill in the art would not question the claimed utility of the compounds described and claimed herein.

As regards Applicants claimed subject matter, Claim 6 is a recitation that the composition (of Claim 1) inhibits the binding of acetylcholine to an acetylcholine receptor in a mammal. This method is not tied to the treatment of a particular disease state or respiratory condition, and is supported in the specification. The second binding assay, page 6, lines 19 to 26 provides for a pan muscarinic antagonism screening against the M1 to M5 acetylcholine receptors, which directly contradicts the Examiner's comments on page 6, 1rst full ¶ that "it is not seen where the instant claims 5-12, for inhibiting the binding of acetylcholine to its receptor in a mammal ... have been enabled by the instant specification." None of the commercially available compounds are 100% selective for any one of the muscarinic receptors, where antagonism of the M3 receptor is most desired for inhaled compounds for treatment of respiratory diseases. The skilled artisan would readily understand the significance of this assay and the potential limitations of compounds tested therein. This is a well known art recognized assay. The method of claim 6 does not require" treatment of a disease state". The claim limitations in Claim 6 are such that a compound of Formula (I) contact a particular receptor and that this contact

is made by a route of administration, e.g. inhalation for receptors in the respiratory tract. In contrast to Claim 6, are Claims 8 and 14 which are specific as to particular respiratory disease states being treated. The Methacholine receptor assay, described in the Specification, page 8, lines 9 to 33 and page 9, lines 1 to 15 support treatment of the disease states as claimed herein.

The specification provides for formulation details, amounts, how to use, and how to administer the claimed dry powder formulations of compounds of Formula (I), and reference additional patents on the various devices for such formulations.

"The enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003), citing *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Clearly, one of ordinary skill in the art would be able to synthesize a wide range of compounds of Formula (I) which are within the scope of the genus. This has been satisfied by the USPTO's allowance of the compounds of Formula (I) in US 2,800,478.

Applicant's invention is the novel use of these compounds as a composition for delivery to the lungs, whether it is via the oral inhalation route or nasal delivery. The application provides a significant discussion on the various inhalers and formulation details therein. Consequently, it is believed that one of ordinary skill in the art is provided with sufficient information to also be able to use the compounds of Formula (I).

There may not even be a requirement to have <u>any</u> working embodiments in order to satisfy the requirements of § 112, first paragraph, even in the chemical arts, as evidenced by the decision in *In re Strahilevitz*, 668 F.2d 1229, 212 U.S.P.Q. 561 (CCPA 1982). In this case, Applicants had described the invention with specificity, but had not disclosed even a single operative embodiment. The court acknowledged that the claims at issue were extremely broad, yet the court reversed the Board's holding of nonenablement, having been persuaded by Strahilevitz that the invention consisted in combining known prior art techniques. Pointing out that § 112 does not require working examples (though they may be desirable in complex technologies), the court found the broad claims enabled throughout their scope. In *Strahilevitz*, Applicants were able to obtain broad claims to methods for removing haptens from blood, despite the fact that no working examples were disclosed, because the evidence of record established that the prior art had taught methods that, when combined together

according to the teachings of the specification, could be used to make the claimed invention.

The MPEP 2164.01(c) on How to Use the Claimed Invention also clearly contemplates that a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, and that 25 USC §112 is thereby satisfied. The state of the art, taken with Applicants specification is sufficient within the context of M3 receptors antagonists to be enabled.

By law a patent application is presumptively enabled when filed. That is, during examination, "[a]s a matter of Patent Office practice . . . a specification . . . must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d at 223, 169 U.S.P.Q. at 369.

Moreover,

> . . . it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224, 169 U.S.P.Q. at 369-70.

Since the PTO bears the initial burden of challenging the presumed utility of an invention, it must produce sufficient evidence that one of ordinary skill in the art would have reason to doubt the claimed utility of the invention.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC §103 is respectfully requested.

CONCLUSION

It is believed that the claims, as amended, are now all in condition for allowance. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed

that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case, the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

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